II. REMARKS/ARGUMENTS

A. Status of Claims

Claim 38, 47, 49, 50, 51, and 52 have been amended without prejudice. Support for the amendments can be found throughout the specification, e.g., on page 23, line 4, to page 30, line 15.

New claims 53-65 have been added. Support for new claims 53 and 54 can be found, e.g., in original claims 38, 49 and 50; and on page 24, line 31, to page 25, line 31, of the original specification. Support for new claims 55 and 60 can be found, e.g., on page 34, lines 11-23, of the original specification. Support for new claim 56 can be found, e.g., on page 22, lines 5-22, of the original specification. Support for new claims 57 and 58 can be found, e.g., on page 25, lines 16-17, of the original specification. Support for new claim 59 can be found, e.g., on page 11 of the original specification. Support for new claim 61 can be found, e.g., on page 38, line 31, of the original specification. Support for new claims 62-65 can be found, e.g., in original claims 38, 47, 49, and 50.

Claims 1-37 and 39-46 were previously cancelled without prejudice.

Claims 38 and 47-65 are currently pending.

Applicants respectfully submit that no new matter has been added by virtue of these amendments.

B. Priority

In the Office Action, the Examiner stated that "[t]he disclosure of the prior-filed applications, Application No. 09/514,354 and provisional application (U.S. 60/059195), fail to provide adequate support or enablement in the manner provided by the first

paragraph of 35 U.S.C. 112 for one or more claims of this application." See Office Action, page 3.

Applicants respectfully disagree. However, Applicants note that claims have been amended without prejudice, and that the Examiner's statement is rendered moot by the amendments to the claims.

C. 35 U.S.C. §103 Rejection over U.S. Patent No. 4,569,937 to Baker et al.; Friedel et al. (Drugs, 1993. Vol. 45(1), pp. 131-156); and Eversmeyer et al. (American Journal of Medicine, Aug. 1993, Vol. 95, pp. 10S-18S).

Claims 38, 47-48 and 50-52 were rejected under 35 U.S.C. §103(a) over U.S. Patent No. 4,569,937 to Baker et al. ("the Baker patent"); Friedel et al. (Drugs, 1993. Vol. 45(1), pp. 131-156); and Eversmeyer et al. (American Journal of Medicine, Aug. 1993, Vol. 95, pp. 10S-18S).

Applicants respectfully submit that independent claim 38 has been amended without prejudice to recite in part "an oral dosage form consisting of (i) nabumetone or at least one pharmaceutically acceptable salt thereof; (ii) oxycodone or at least one pharmaceutically acceptable salt thereof; and (iii) and at least one pharmaceutically acceptable excipient." (emphasis added).

Applicants further submit that a dosage form suggested by the combination of the cited references would necessarily contain ibuprofen, because without ibuprofen the purpose of the Baker patent, entitled ANALGESIC MIXTURE OF OXYCODONE AND IBUPROFEN and utilizing ibuprofen in every example, would be frustrated.

In this regard, Applicants note that the Baker patent states that "unexpectedly enhanced analgesic activity of combination of oxycodone and ibuprofen" is the activity that is "**greater that the activity expected from the sum of the activities of individual components.**" See column 3, lines 22-26 (emphasis added). Accordingly, Applicants

submit that when considered as a whole, the effect contemplated by the Baker patent is not merely additive, but unexpectedly synergistic.

Manual of Patent Examining Procedure states that "... [i]f proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification") See, e.g., MPEP, Section 2143.01.

Applicants notes that ibuprofen is excluded from the scope of amended claim 38, by virtue of "consisting of" language.

Accordingly, Applicants submit that the combination of the cited references would not have suggested to one skilled in the art "an oral dosage form consisting of (i) nabumetone or at least one pharmaceutically acceptable salt thereof; (ii) oxycodone or at least one pharmaceutically acceptable salt thereof; and (iii) and at least one pharmaceutically acceptable excipient" as recited in the present claims, because the claimed dosage form excludes ibuprofen, and therefore, renders the Baker patent unsuitable for its intended purpose- i.e., pharmaceutical compositions of narcotic analgesics and ibuprofen exhibiting synergistic analgesic activity.

Applicants also submit that the combination of the cited references would not have suggested to one skilled in the art "an oral dosage form consisting of (i) nabumetone or at least one pharmaceutically acceptable salt thereof; (ii) oxycodone or at least one pharmaceutically acceptable salt thereof; and (iii) and at least one pharmaceutically acceptable excipient" as recited in the present claims, because none of the cited references teach or suggest "an oral dosage form consisting of (i) nabumetone or at least one pharmaceutically acceptable salt thereof; (ii) oxycodone or at least one pharmaceutically acceptable salt thereof; and (iii) and at least one pharmaceutically acceptable excipients" as recited in the present claims.

Further, Manual of Patent Examining Procedure states that

> *The examiner bears the initial burden of* ***factually*** *supporting any prima facie conclusion of obviousness. If, however, the examiner does not produce a prima facie case, the applicant is under no obligation to submit evidence of nonobviousness.*

See, MPEP, Section 2142. (emphasis added).

In the present case, the Examiner has not articulated what would have suggested to one skilled in the art to (i) pick nabumetone out of, e.g., other COX-2 inhibitors having similar properties to nabumetone, (ii) disregard the teachings of the Baker patent and replace ibuprofen, the essential ingredient of the Baker patent combination, with nabumetone, and (iii) expect the resulting combination to produce a synergistic analgesic effect as mandated by the Baker patent.

In particular, the Examiner has not articulated what would have prompted one skilled in the art to select nabumetone for inclusion in the combination with oxycodone instead of, e.g., "celecoxib (SC-58635), DUP-697, flosulide (CGP-28238), meloxicam, 6-methoxy-2 naphthylacetic acid (6-MNA), Vioxx (rofecoxib) (MK-966), ... nimesulide, NS-398, SC-5766, SC-58215, T-614" and other COX-2 inhibitors in the development as of mid-1998, all regarded to have "a reduced potential for gastrointestinal toxicity, a reduced potential for renal side effects, a reduced effect on bleeding time and a lessened ability to induce asthma attacks in aspirin-sensitive asthmatic subjects", as compared to traditional NSAIDs (e.g., ibuprofen) at the time the present application was filed. See e.g., page 13 of the present specification.

The Examiner has also not articulated what would have suggested to one skilled in the art to look to the Friedel et al. (Drugs, 1993. Vol. 45(1), pp. 131-156); and Eversmeyer et al., and pick these references, instead of references directed to other COX-2 inhibitors, having similar properties to nabumetone, e.g., COX-2 inhibitors articulated above.

Applicants further submit that MPEP states that "... Office personnel **must** articulate ... a finding that one of ordinary skill in the art would have recognized that the results of the combination were predictable." See MPEP, section 2143. (emphasis added).

Applicants respectfully submit that in order to for the one skilled in the art to even consider modifying the combination of the Baker patent by replacing ibuprofen with nabumetone in view of the cited references, the cited references would have to at least indicate that the combination of nabumetone and oxycodone would also result in a synergistic effect, as the effect contemplated by the combination of the Baker patent is synergistic for the reasons set forth above. However, the cited references do not suggest that the analgesic effect of the combination of nabumetone and oxycodone would be synergistic.

With regard to the Examiner's reference to column 1, lines 23-25, of the background section of the Baker patent where it is stated that "the analgesic effect of the combination of a selected NSAID and a selected analgesic is greater that for either alone," Applicants respectfully submit that this passage does not suggest a synergistic effect, but merely an additive effect.

The Examiner has also failed to provide any factual evidence for showing synergistic effect of the combination (i.e., isobologram for the interaction of oral oxycodone and nabumetone).

Accordingly, Applicants submit that the Examiner has not shown and articulated a finding that the results of the suggested combination (e.g., a synergistic analgesic effect) would be predictable to one skilled in the art, as required by the MPEP.

Applicants respectfully assert that, in the absence of these findings, the obviousness rejection is not factually supported enough to establish the *prima facie* case of obviousness. See, MPEP, Section 2142.

Further, Applicants respectfully note that the only NSAID utilized in the invention of the Baker patent, the patent entitled ANALGESIC MIXTURE OF OXYCODONE AND IBUPROFEN and utilizing ibuprofen in every example, is ibuprofen. See e.g., column 1, lines 6 - 9 ("[t]his invention relates to pharmaceutical compositions of narcotic analgesics and **ibuprofen** having analgesic activity in mammals, and to methods of use of the compositions to alleviate pain in mammals") (emphasis added); *see also* column 2, lines 11-15 ("[a]ccording to the present invention there is provided a pharmaceutical composition comprising a combination of (a) a narcotic analgesic, or a pharmaceutically acceptable salt thereof, and (b) **ibuprofen**, or a pharmaceutically suitable salt thereof ... ") (emphasis added); *see also* Figure 1 ("ISOBOLOGRAM FOR THE INTERACTION OF ORAL OXYCODONE HCL AND **IBUPROFEN**") (emphasis added); *see also* column 1, line 1 & 2 ("ANALGESIC MIXTURE OF OXYCODONE AND **IBUPROFEN**") emphasis added; *see also* column 2, lines 20-24 (" ... synergistically effective analgesic amounts of oxycodone, or a pharmaceutically suitable salt thereof, and **ibuprofen**, or a pharmaceutically suitable salt thereof...") (emphasis added); *see also* column 2, line 34 and 35 ("... various dose ratios of oxycodone and **ibuprofen**); *see also* column 2, lines 64 and 65 ("[i]n a composition of the invention, oxycodone and **ibuprofen** are combined ...) (emphasis added); see also column 3, lines 23 and 24 ("... unexpectedly enhanced analgesic activity of combinations of oxycodone and **ibuprofen**") (emphasis added); *see also* column 3, lines 53-56 ("... the active ingredient is administered at a daily dosage of from about 0.05 to 7.50 milligrams per kilogram (mg/kg) of body weight of oxycodone and from about 10 to 120 mg/kg of **ibuprofen**") (emphasis added); *see also* Examples 1-24, all utilizing ibuprofen.

Therefore, Applicants submit that the "selected NSAID" of the Baker patent, when the Baker patent is considered as a whole, is ibuprofen.

Accordingly, as stated above, Applicants submit that a dosage form suggested by the combination of the cited references would necessarily contain ibuprofen, and that replacing ibuprofen with nabumetone would render the Baker patent unsuitable for its

intended purpose (i.e., provision of a synergistic analgesic combination of a narcotic analgesic and ibuprofen).

Further, as discussed above, ibuprofen is excluded from the dosage form of independent claim 38.

Accordingly, Applicants submit that even if a *prima facie* case of obviousness has been established (a position which is traversed), the combination of the cited references still would not have suggested to one skilled in the art "an oral dosage form consisting of (i) nabumetone or at least one pharmaceutically acceptable salt thereof; (ii) oxycodone or at least one pharmaceutically acceptable salt thereof; and (iii) at least one pharmaceutically acceptable excipient" as recited in the present claims, because the proposed modification would render the Baker patent unsuitable for its intended purpose. See, e.g., MPEP, Section 2143.01. "... [i]f proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification ...").

Accordingly, withdrawal of the rejection of claim 38 and claims 47-48 and 50-52 which depend therefrom is respectfully requested.

In the event, the Examiner seeks to maintain the rejection based on the combination of the cited references, Applicants respectfully request that the missing reasons and evidence (as pointed out above) be provided to factually support the rejection as required by the MPEP, and to allow Applicants to properly evaluate the basis for the Examiner's positions and respond appropriately. See, MPEP, Section 2142.

D. 35 U.S.C. 103 (a) Rejection over Baker et al., Friedel et al. and Eversmeyer et al. in view of Oshlack et al. (US 5,472,712) or Oshlack et al. (US 6,294,195)

Claim 49 was rejected under 35 U.S.C. § 103(a) over the Baker patent, Friedel et al. and Eversmeyer et al., and Oshlack et al. (US 5,472,712) or Oshlack et al. (US 6,294,195).

Claim 49 depends from claim 38. Claim 38 was discussed above.

Applicants submit that, for the reasons discussed above, the combination of the cited references would not have suggested to one skilled in the art "an oral dosage form consisting of (i) nabumetone or at least one pharmaceutically acceptable salt thereof; (ii) oxycodone or at least one pharmaceutically acceptable salt thereof; and (iii) at least one pharmaceutically acceptable excipient" as recited in claim 38, because the proposed modification would render the Baker patent unsuitable for its intended purpose. See, e.g., MPEP, Section 2143.01. "... [i]f proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification ...").

Accordingly, Applicants respectfully submit that claim 38 is not rendered obvious by the combination of the cited references. Applicants submit that claim 49 which depends from claim 38, and includes the features of claim 38, is also not rendered obvious by the combination of the cited references. See, e.g., *In re Fine*, 837 F.2d. 1071 (Fed. Cir. 1988) ("Dependent claims are nonobvious under section 103 if the independent claims from which they depend are nonobvious. *Hartness Int'l, Inc. v. Simplimatic Eng'g Co.*, 819 F.2d 1100, 1108, 2 USPQ2d 1826, 1831 (Fed.Cir.1987); *In re Abele,* 684 F.2d 902, 910, 214 USPQ 682, 689 (CCPA 1982); *see also In re Sernaker,* 702 F.2d 989, 991, 217 USPQ 1, 3 (Fed.Cir.1983)").

Accordingly, withdrawal of the rejection is respectfully requested.

E. Rejection under 35 U.S.C. § 112, first paragraph

Claims 38 and 47-52 were rejected under 35 U.S.C. § 112, first paragraph, for containing the language "an oral dosage form comprising two analgesic compounds and/or pharmaceutically acceptable salts thereof consisting of (i) nabumetone ... and (ii) oxycodone ..." in independent claim 38.

Claim 38 has been amended without prejudice to remove the objected language.

Accordingly, withdrawal of the rejection is respectfully requested.

F. Rejection under 35 U.S.C. § 112, second paragraph

Claims 38 and 47-52 were rejected under 35 U.S.C. § 112, second paragraph, for containing the language "an oral dosage form comprising two analgesic compounds and/or pharmaceutically acceptable salts thereof consisting of (i) nabumetone ... and (ii) oxycodone ..." in independent claim 38.

Claim 38 has been amended without prejudice to remove the objected language.

Accordingly, withdrawal of the rejection is respectfully requested.

G. Rejection under 35 U.S.C. § 102(b) over U.S. Patent No. 5,840,731

Claims 38, 47-50 and 52 were rejected under 35 U.S.C. § 102(b) over U.S. Patent No. 5,840,370 to Mayer et al.

Independent claim 38 has been amended without prejudice to recite in part "an oral dosage form consisting of (i) nabumetone or at least one pharmaceutically acceptable salt thereof; (ii) oxycodone or at least one pharmaceutically acceptable salt thereof; and (iii) at least one pharmaceutically acceptable excipient."

Applicants submit that the Mayer patent does not teach "an oral dosage form consisting of (i) nabumetone or at least one pharmaceutically acceptable salt thereof; (ii) oxycodone or at least one pharmaceutically acceptable salt thereof; and (iii) at least one pharmaceutically acceptable excipient", as the dosage form in accordance with the Mayer patent would necessarily include "a nontoxic N-methyl-D-aspartate (NMDA) receptor antagonist." However, the presence of "a nontoxic N-methyl-D-aspartate (NMDA) receptor antagonist" is excluded from the scope of independent claim 38, by virtue of the "consisting of" language.

Accordingly, Applicants submit that the Mayer patent does not anticipate claims 38 and claims dependent therefrom, and respectfully request withdrawal of the rejection.

III. CONCLUSION

An early and favorable action on the merits is earnestly solicited. The Examiner is respectfully requested to contact the undersigned at the telephone number provided below in the event that a telephonic interview will advance the prosecution of the application.

Respectfully submitted,
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